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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/032,972	02/26/98	KROTZ	A ISIS-2710

HM12/0831

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EXAMINER	
CRANE, L	
ART UNIT	**PAPER NUMBER**
1623	9

DATE MAILED: 08/31/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)	
09/032,972	Krotz et al.	
Examiner	Group Art Unit	
L. E. Crane	1623	

—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE ----3---- MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

☒ Responsive to communication(s) filed on 07/09/99 (Amdt A).

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle,* 1935 C.D. 1 1; 453 O.G. 213.

Disposition of Claims

☒ Claim(s) 1-41 is/are pending in the application.

Of the above claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1-41 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119 (a)-(d)

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 11 9(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 1 7.2(a)).

*Certified copies not received: _____.

Attachment(s)

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☒ Notice of Reference(s) Cited, PTO-892

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Interview Summary, PTO-413

☐ Notice of Informal Patent Application, PTO-152

☐ Other _____

Office Action Summary

The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group 1600, Art Unit 1623.

No claims have been cancelled and the amendments filed July 9, 1999 have been entered.

Claims **1–41** remain in the case.

Claims **2, 6–7, 22, 24–25 and 38** are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claims **2 and 22**, the added step is not completely described because the proper placement of the added step within the sequence of steps of the previous claim has not been specified.

Applicant's arguments filed July 9, 1999 have been fully considered but they are not persuasive.

Applicant argues at p. 10 of the instant response that the standard of capping step in oligonucleotide synthesis "occurs before or after oxidation or sulfurization." Examiner agrees, but notes that applicant is claiming a process for oligonucleotide synthesis which is alleged different from the prior art. The difference or similarity of the instant claimed process when compared with the prior art as regards claims **2 and 22** and the placement of "the capping step" within the overall oligonucleotide synthesis is not determinable by

inspection of the noted claims. For this reason the instant rejection has been maintained.

In claims **6-7, 24-25 and 38**, the terms "*o-, [m]-* or *p-* xylene" and "*o-, [m]-* and *p-*xylene" are missing a prefix italic letter "m" and each is an incorrect portion of a Markush group by including the term "or" or the extra term "and." Applicant is respectfully requested to substitute the term -- o-xylene, m-xylene, p-xylene -- in each instance.

Applicant's arguments with respect to claim(s) **6-7, 24-25 and 38** have been considered but are moot in view of the new grounds of rejection.

In claims **13 and 30**, line 7, the term "triclhoroethyl" is a technical misspelling.

Applicant's arguments with respect to claim(s) **13 and 30** have been considered but are moot in view of the new grounds of rejection.

The following is a quotation of 35 U.S.C. §103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> "A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made."

Claims **1-41** are rejected under 35 U.S.C. §103(a) as being unpatentable over Ravikumar '621 (PTO-892 ref. **A**) in view of Caruthers et al. '679 (PTO-892 ref. **G**) and further in view of Froehler et al. '076 (PTO-892 ref. **H**) and further in view of Sproat et al. (PTO-892 ref. **W**), Conway et al. (PTO-892 ref. **Y**), Atkinson et al. (PTO-892 ref. **Z**), and Sproat et al. (PTO-892 ref. **RA**).

The instant claims are directed to entirely conventional oligonucleotide syntheses wherein the only variation from the prior art is the choice of solvent or solvent mixture to be used therein.

Ravikumar '621 (PTO-892 ref. **A**) discloses entirely conventional oligonucleotide synthesis wherein the solvent is acetonitrile and the P-protecting group varies from the conventional. This reference does not disclose the particular mixture of solvents selected for use in the instant claimed processes.

Caruthers et al. '679 (PTO-892 ref. **G**) at column 5, lines 10-14, teaches the use of "... any solvent which will dissolve the reactants ..." including a list of specific organic solvents for phosphoramidite-intermediate-based oligonucleotide synthesis. This reference does not disclose the particular mixture of solvents selected for use in the instant claimed processes.

Froehler et al. '076 (PTO-892 ref. **H**) discloses the use of H-phosphonate intermediates for the synthesis of oligonucleotides and phosphorothioate analogues thereof. This reference also teaches the use of " ... an anhydrous organic solvent, preferably pyridine/acetonitrile ...," at column 5, lines 26-28. This reference

does not disclose the particular mixture of solvents selected for use in the instant claimed processes.

Sproat et al. (PTO-892 ref. **W**) discloses at p. 52, (lines 2 and 18) that toluene is useful for the purification of synthetic nucleoside intermediates. Additionally, this reference discloses at pp. 64 (Protocol 17, step 3) and page 70 (Protocol 25, step 4) that benzene is a solvent for the key oligonucleotide synthesis reagents, nucleoside-3'-O-phosphoramidites, and may be used to co-evaporate triethylamine therefrom.

Conway et al. (PTO-892 ref. **Y**) is directed to the chemical synthesis of labeled DNA and at p. 218, Section C, Subsection 2, discloses the specific use of toluene as an effective solvent for dissolution of pyridine-contaminated dinucleoside monophosphorothioate d[Cp(s)C] prior to co-evaporative removal of the pyridine/toluene mixture therefrom. The instant reference does not disclose that toluene is used in the coupling step required to make this compound.

Atkinson et al. (PTO-892 ref. **Z**) discloses at p. 43 in section (xvii), that toluene is useful to dissolve the 3'-O-phosphoramidites of 2'-deoxyadenosine, 2'-deoxycytidine, and 2'-deoxyuridine as the first step in a re-precipitation process. This reference also teaches at p. 76, section 7.5, "Variation in Procedures," although no specific teaching of the substitution of an aromatic solvent from other solvents used in oligonucleotide synthesis is present. In section 8.7 at p. 80, "toluene" is listed as a reagent useful in the preparation of "Deoxyribonucleoside-derivatized supports." This reference at the

noted locations does not disclose the particular set of solvents claimed herein as useful in the coupling step of an oligonucleotide synthesis.

Sproat et al. (PTO-892 ref. **RA**).at p. 84, lines 10 and 9 from the end of the page, discloses that the "[p]urity of solvents and reagents is of the utmost importance as far as reliability and reproducibility of the [oligonucleotide synthetic] method are concerned." This reference also discloses at p. 93, section (xv), that a di-protected adenosine derivative may be effectively dissolved in toluene prior to evaporative solvent removal for the purpose of co-evaporating residues of pyridine therefrom (see also p. 96, section (vi) for a similar disclosure). Additionally, at p. 111, section 7.6, the listing of solvents useful in oligonucleotide synthesis includes both benzene and toluene. This reference at the noted locations does not disclose the particular set of solvents claimed herein as useful in the coupling step of an oligonucleotide synthesis.

The teachings of the prior art Caruthers and Froehler references motivate the selection of practically any organic solvent or solvent mixtures which will dissolve the reactants. As all three references provide descriptions of conventional prior art processes for making oligonucleotides via phosphoramidite or H-phosphonate intermediates including all of the process steps included within the instant claims, the choice of a particular solvent or solvent mixture as taught and motivated by Caruthers and also by Froehler is a variable clearly within the purview of the ordinary practitioner seeking to optimize the process of oligonucleotide synthesis regardless of the particular type of synthetic intermediate selected. The Sproat et al. (W), Conway et al., Atkinson et al., and Sproat et al.(RA) references are each generally directed to oligonucleotide synthesis

and provide disclosures that at least two different nucleoside-3'-O-phosphoramidites, at least one dinucleotide derivative, and some nucleoside derivatives m ay be effectively dissolved in benzene and/or toluene, disclosures which are deemed to provide a factual motivation for the ordinary practitioner conducting routine experimentation to substitute toluene, benzene or their aromatic solvent relatives as substitutes for at least a portion of the standard solvent (THF, acetonitrile, etc.) typically used during the coupling step in oligonucleotide synthesis, presumably in order to minimize the cost of the process. For this reason the instant process claims are deemed to be lacking in any patentable distinction in view of the noted prior art.

Therefore, the instant claimed oligonucleotide processes would have been obvious to one of ordinary skill in the art having the above cited references before him at the time the invention was made.

Applicant's arguments with respect to claim(s) **1-41** have been considered but are moot in view of the new grounds of rejection.

References made of record but not cited above are deemed to be either equivalents to the cited references or to be of interest as closely related prior art which shows the state of the relevant prior art.

Papers related to this application may be submitted to Group 1600 via facsimile transmission(FAX). The transmission of such papers must conform with the notice published in the Official Gazette (1096 OG 30, November 15, 1989). The telephone numbers for the

FAX machines operated by Group 1600 are **(703) 308-4556** and **703-305-3592** .

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner L. E. Crane whose telephone number is 703-**308-4639** . The examiner can normally be reached between 9:30 AM and 5:00 PM, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor can be reached at (703)-308-1235.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1600 receptionist whose telephone number is 703-**308-1235** .

LECrane:lec
8/26/99

L. Erie Crane
Patent Examiner
Group 1600